PATENT SPECIFICATION

1,163,103

NO DRAWINGS

1,163,103

Date of Application (No. 49924/66) and filing Complete Specification: 8 Nov., 1966.

Application made in United States of America (No. 507,718) on 15 Nov., 1965.

Complete Specification Published: 4 Sept., 1969.

Index at acceptance:—C2 C(3C5A4, 3C5C3, 3C5C5, 3C5E1, 3C5E2, 3ABA4A4, 3B4A4F1, 1E5K4, 1E3K4, 1E3K6, 3A10E4B3, 3A10E5E, 3A7V2A4, 3A7V2E1, 3A7V2K3B, 3A7V1A4, 3A7V1E2, 3A7VF1, 3A7V1F2, 3A7V1J1, 3A7V1K3B, 3A7V1P, LH30Y, LH309, LH602, LH790, 173—198—289, 177—271—279, LK173, LK177, LK198, LK214, LK215, LK247, LK25Y, LK250, LK252, LK253, LK271, LK279, LK28X, LK289, LK30Y, LK32Y, LK321, LK322, LK351, LK352, LK36Y, LK360, LK361, LK362, LK363, LK652, LK670, LK672, LK761, LK762, LK766, LK790, 173—198—289, 177—271—279)

International Classification:—C07 d 99/04

ERRATUM

SPECIFICATION NO. 1,163,103

Page 1, For Index at Acceptance C2C only read:- (1E3K4, 1E3K6, 1E5K4, 3A7V1A4, 3A7V1E2, 3A7V1F1, 3A7V1F2, 3A7V1J1, 3A7V1K3B, 3A7V1P, 3A7V2A4, 3A7V2E1, 3A7V2K3B, 3A10E4B3, 3A10E5E, 3A12A4A, 3A12A4B, 3A12B2, 3A12B4, 3A12C4, 3A13A4A4, 3A13A4F1, 3C5A4, 3C5C3, 3C5C5, 3C5E1, 3C5E2, 214, 215, 22Y, 220, 247, 25Y, 250, 252, 253, 28X, 30Y, 32Y, 321, 322, 323, 34Y, 342, 351, 352, 36Y, 360, 361, 362, 363, 366, 368, 45Y, 450, 50Y, 509, 595, 598, 601, 603, 62X, 63X, 648, 65X, 652, 668, 67X, 670, 672, 680, 682, 761, 762, 766, 790, 173-198-289, 177-271-279, KK, KM, KY, LH, LK)

THE PATENT OFFICE,
5th February 1970

D 121734/21

COMPLETE SPECIFICATION

Ribofuranosyl Purine Derivatives

We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns 2,6-substituted purine-3′-alkyl nucleosides and processes for their preparation.

SEE ERRATA SLIP ATTACHED.

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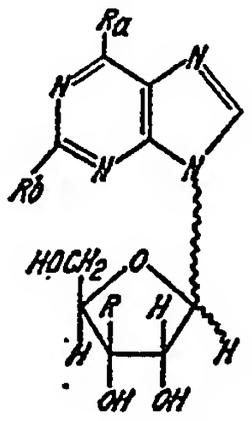
This invention concerns 2,6-substituted purine-3'-alkyl nucleosides and processes for their preparation.

[Pric

SEE ERRATA SLIP ATTACHED.

The compounds in accordance with the present invention have the formula:—



I

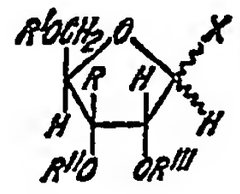
where R is a C_{1-5} alkyl radical and each of R_a and R_b is a hydrogen or halogen atom or a hydroxy, C_{1-5} alkyl, amino, C_{1-5} alkylamino, di(C_{1-5} alkyl)amino, mercapto or C_{1-5} alkyl mercapto radical.

In preferred compounds R is a methyl or ethyl radical.

Compounds of the present invention may be used in the preparation of various 3'-C_{1-5} alkyl nucleotides by their reaction with phosphorus compounds. These nucleotides may be useful in the study of nucleic acid metabolism.

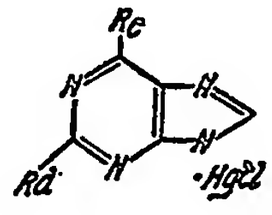
Among specific values of R_a and R_b in the compounds I of the present invention apart from those mentioned already, are, methyl, ethyl, propyl, methylamino, dimethylamino, ethylamino, diethylamino, propylamino, dipropylamino, chlorine, bromine, iodine, methyl mercapto, ethyl mercapto, and propyl mercapto.

The compounds of the present invention are prepared in general by a two-step process. The first step in this process, Step A, is carried out by treating a 2,3,5-tri-O-acyl-3-C_{1-5}alkyl-*D*-ribofuranosyl halide of the formula:—



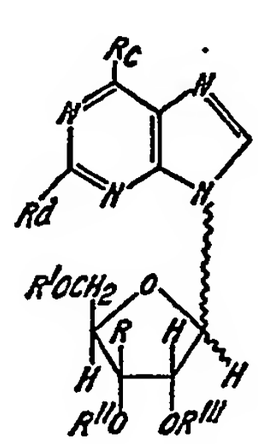
II

with a chloromercuri 2,6-substituted purine of the formula:—



III

to form a 9-(2,3,5-tri-O-acyl-3-C_{1-5} alkyl-*D*-ribofuranosyl)-2,6-substituted purine intermediate of the formula:—



IV

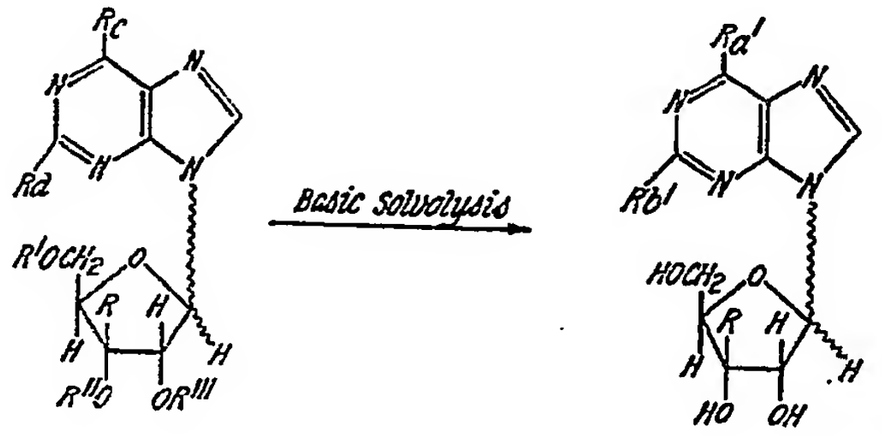
where R is a C_{1-5} alkyl radical, each of R_c and R_d is a halogen or hydrogen atom or a hydroxy, C_{1-5} alkyl, acylamino or acyl C_{1-5} alkylamino radical, each of R', R'', and R''' is an acyl group and X is a halogen atom. The reaction should be carried out at a temperature of from 25° to 150°C., preferably from 100° to 140°C., for a

period of time sufficient to complete the reaction. This time is usually from about 15 minutes to about 5 hours. It should be noted that the higher the reaction temperature, the quicker the reaction will be complete. The 2,3,5-tri-O-acyl-3-alkyl-*D*-ribofuranosyl halides may be prepared by reacting a 5-O-acyl-1,2-O-isopropylidene-*D-erythro*-3-pentulofuranose with a Grignard reagent thereby forming a 5-O-acyl-1,2-O-isopropylidene 3-C_{1-5} alkyl-*D*-ribofuranose which is subjected to acidic alcoholysis to produce an alkyl 5-O-acyl-3-C_{1-5} alkyl-*D*-ribofuranoside which is acylated to an alkyl 2,3,5-tri-O-acyl-3-C_{1-5} alkyl-*D*-ribofuranside and converted to the ribofuranosyl halide by a halogenation replacement reaction in an appropriate solvent.

2,3,5-Tri-O-acyl-3-alkyl-*D*-ribofuranosyl halides and 5-O-acyl-1,2-O-isopropylidene-3-alkyl-α-*D*-ribofuranoses are claimed in our copending application No. 49923/66 (Serial No. 1,163,102).

The compounds of the present invention having the Formula I′ below, where each of R_a' and R_b' is a hydrogen or halogen atom or a hydroxy, C_{1-5} alkyl, amino or C_{1-5} alkyl amino radical are prepared by basic solvolysis of the 9-(2,3,5-tri-O-acyl-3-C_{1-5} alkyl-*D*-ribofuranosyl)-2,6-substituted purine intermediate compounds (Formula IV′).

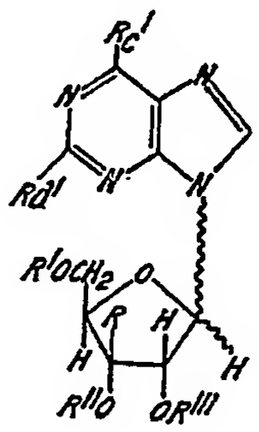
This reaction is illustrated as follows:—



IV′ I′

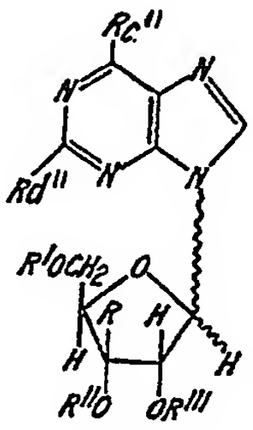
where R_a', R_b', R_c, R_d, R, R′, R″, and R‴ are as defined above. When R_c or R_d in the starting material is an acylamino or acyl C_{1-5} alkylamino radical it is converted to an amino or C_{1-5} alkylamino radical during the course of the reaction.

The compounds in accordance with the present invention in which at least one R_a and R_b is a hydrogen atom can also be prepared by reacting a compound of the formula:—



IV″

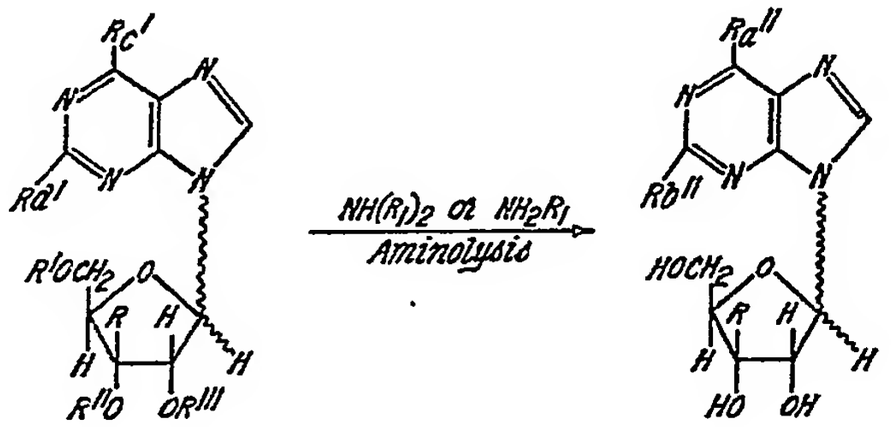
where R, R′, R″ and R‴ are as defined above and R_c' and R_d' are as defined for R_c and R_d provided that at least one of R_c' and R_d' is a halogen atom, with hydrogen in the presence of a catalyst to produce a compound of the formula:—



where R, R′, R″ and R‴ are as defined above, one of R_c'' and R_d'' is a hydrogen atom and the other of R_c'' and R_d'' is a hydrogen atom or a hydroxy, C_{1-5} alkyl, acylamino or acyl C_{1-5} alkylamino radical, followed by basic solvolysis to remove the R′, R″ and R‴ acyl groups and convert any acylamino or acyl C_{1-5} alkylamino groups present as R_c'' or R_d'' to amino or C_{1-5} alkylamino groups.

The compounds of the invention having the Formula I″ below, where either or both of R_a'' and R_b'' is a C_{1-5} alkylamino or di(C_{1-5} alkyl)amino radical, are prepared by aminolysis of the 9-(2,3,5-tri-O-acyl-3-alkyl-*D*-ribofuranosyl)-2,6-substituted purine intermediate compounds (IV″ below) in which the 2,6 purine positions are substituted in either or both positions with a halogen atom.

The reaction is illustrated as follows:—

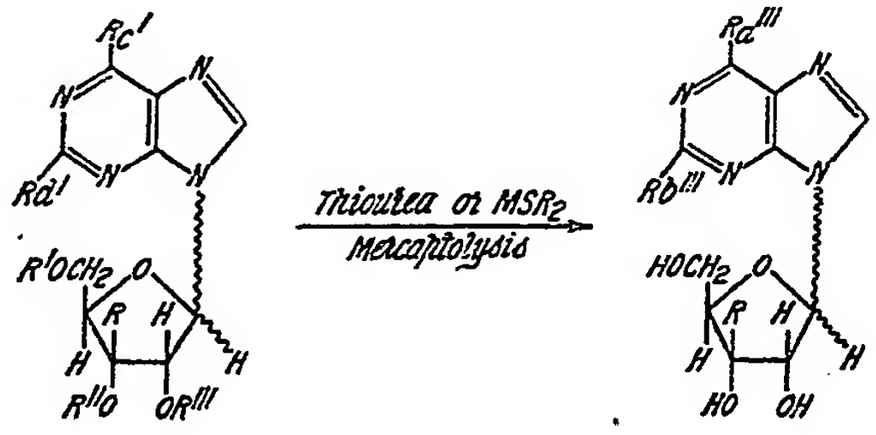


IV″ I″

where R, R′, R″, R‴, R_c', R_d', are as defined above, R_1 is a C_{1-5} alkyl radical, one of R_a'', and R_b'' is a C_{1-5} alkylamino or di(C_{1-5} alkyl)amino and the other of R_a'' and R_b'' is a hydrogen atom or a hydroxy, C_{1-5} alkyl, amino, C_{1-5} alkylamino or di(C_{1-5} alkyl)amino radical. When R_c' or R_d' in the starting material is an acylamino or acyl S_{1-5} alkylamino radical it is converted to an amino or C_{1-5} alkylamino group during the course of the reaction.

The compounds of the invention having the Formulas I‴, where either or both of R_a''' and R_b''' is a mercapto or C_{1-5} alkyl mercapto radical are prepared by mercaptolysis of a compound of formula IV″.

The reation is illustrated as follows:—



IV″ I‴

where R, R′, R″, R‴, R_c' and R_d' are as defined above, R_2 is a C_{1-5} alkyl radical,

one of R_a''' and R_b''' is a mercapto or C_{1-5} alkyl mercapto radical and the other of R_a''' and R_b''' is a hydrogen atom or a hydroxy, C_{1-5} alkyl, amino, C_{1-5} alkylamino, mercapto or C_{1-3} alkylmercapto radical.

When R_c' or R_d' in the starting material is acylamino or acyl C_{1-5} alkylamino it is converted to an amino or C_{1-5} alkylamino group during the course of the reaction.

When the mercaptolysis reactant is thiourea the acyl blocking groups R′, R″ and R‴ are not removed and the resulting intermediate must be subjected to basic solvolysis in order to obtain the compounds of the present invention, compound I‴.

In general, the process of the present invention involves reacting a chloro-mercuri 2,6-substituted purine with 2,3,5-tri-O-acyl-3-C_{1-5} alkyl ribofuranosyl halide to form a 9-(2,3,5-tri-O-acyl-3-C_{1-5} alkyl-D-ribofuranosyl)-2,6-substituted purine. These intermediate compounds are then either solvolysed, aminolysed, mercaptolysed, or hydrogenated and solvolysed to form the compounds of the present invention. When mercaptolysis is carried out using thiourea, a further step of solvolysis must follow in order to obtain the compounds of the present invention.

Preferably, the compounds of the present invention are obtained by reaction, in Step A, of a chloro-mercuric 2,6-substituted purine with a 2,3,5-tri-O-acyl-3-(C_{1-5} alkyl)-D-ribofuranosyl halide, essentially stoichiometrically at a temperature of from 25°C. to 150°C. and preferably from 100°C. to 140°C. in an appropriate solvent. The selection of the solvent is not important as long as it is an inert solvent boiling in the range of 25°C. to 150°C. Examples of such solvents are benzene, dibutyl ether, cyclohexane, toluene and xylene, preferably toluene or xylene. The reaction is normally complete in from about 15 minutes to about 5 hours depending on the selection of the reaction temperature. After obtaining the intermediate reaction product in Step A, these compounds are then either solvolysed, aminolysed, mercaptolysed, or hydrogenated and solvolysed in Step B depending upon the desired 2,6-substitutions in the purine portions of the compounds.

In the case of solvolysis, the reaction may be carried out in the presence of a basic catalyst in an appropriate solvent at a temperature of from 5°C. to 150°C. preferably from 65°C. to 90°C. in a reaction time of from about 15 minutes to about 5 hours. The length of reaction time is dependent upon the temperature, the catalyst and the solvent. Examples of basic catalysts are alkali and alkaline-earth metal hydroxides and their corresponding alkoxides, solutions of ammonia, amines and substituted amines. Examples of the solvents are C_{1-4} alcohols. The preferred solvent is methanol.

In the case of aminolysis, the reaction may be carried out in the presence of a monoC_{1-5} alkyl or a di(C_{1-5} alkyl)amine at a temperature of from 25°C. to 150°C. and preferably from 85°C. to 110°C. in a reaction time of from about 15 minutes to about 5 hours. Examples of suitable amines are methylamine, dimethylamine, ethylamine, diethylamine, propylamine and dipropylamine.

In the case of mercaptolysis, the reaction may be carried out in the presence of thiourea or a metal salt of a C_{1-5} alkyl mercaptan in a temperature range of from about 25°C. to about 150°C. and preferably about 65°C. to about 90°C. in a reaction time of from about 15 minutes to about 5 hours. Examples of the alkali or alkaline earth metal salts of C_{1-5} alkyl mercaptans are sodium methylmercaptan, sodium ethylmercaptan, sodium isopropylmercaptan, potassium methylmercaptan and calcium methylmercaptan.

In the case of hydrogenation the catalyst is preferably palladium on charcoal.

Representative of the novel compounds of the present invention are

9-(3-methyl-D-ribofuranosyl)-2-methylpurine
9-(3-methyl-D-ribofuranosyl)-6-methylpurine
9-(3-methyl-D-ribofuranosyl)-2,6-dimethylpurine
9-(3-methyl-D-ribofuranosyl)-2-ethylpurine
9-(3-methyl-D-ribofuranosyl)-6-ethylpurine
9-(3-methyl-D-ribofuranosyl)-2,6-diethylpurine
9-(3-methyl-D-ribofuranosyl)-2-propylpurine
9-(3-methyl-D-ribofuranosyl)-6-propylpurine
9-(3-methyl-D-ribofuranosyl)-2,6-dipropylpurine
9-(3-ethyl-D-ribofuranosyl)-2-methylpurine
9-(3-ethyl-D-ribofuranosyl)-6-methylpurine
9-(3-ethyl-D-ribofuranosyl)-2,6-dimethylpurine
9-(3-ethyl-D-ribofuranosyl)-2-ethylpurine
9-(3-ethyl-D-ribofuranosyl)-6-ethylpurine
9-(3-ethyl-D-ribofuranosyl)-2,6-diethylpurine

9-(3-ethyl-D-ribofuranosyl)-2-propylpurine
9-(3-ethyl-D-ribofuranosyl)-6-propylpurine
9-(3-ethyl-D-ribofuranosyl)-2,6-dipropylpurine
9-(3-propyl-D-ribofuranosyl)-2-methylpurine
9-(3-propyl-D-ribofuranosyl)-6-methylpurine
9-(3-propyl-D-ribofuranosyl)-2,6-dimethylpurine
9-(3-propyl-D-ribofuranosyl)-2-ethylpurine
9-(3-propyl-D-ribofuranosyl)-6-ethylpurine
9-(3-propyl-D-ribofuranosyl)-2,6-diethylpurine
9-(3-propyl-D-ribofuranosyl)-2-propylpurine
9-(3-propyl-D-ribofuranosyl)-6-propylpurine
9-(3-propyl-D-ribofuranosyl)-2,6-dipropylpurine
9-(3-methyl-D-ribofuranosyl)-2-aminopurine
9-(3-methyl-D-ribofuranosyl)-6-aminopurine
9-(3-methyl-D-ribofuranosyl)-2,6-diaminopurine
9-(3-ethyl-D-ribofuranosyl)-2-aminopurine
9-(3-ethyl-D-ribofuranosyl)-6-aminopurine
9-(3-ethyl-D-ribofuranosyl)-2,6-diaminopurine
9-(3-propyl-D-ribofuranosyl)-2-aminopurine
9-(3-propyl-D-ribofuranosyl)-6-aminopurine
9-(3-propyl-D-ribofuranosyl)-2,6-diaminopurine
9-(3-methyl-D-ribofuranosyl)-2-methylaminopurine
9-(3-methyl-D-ribofuranosyl)-6-methylaminopurine
9-(3-methyl-D-ribofuranosyl)-2,6-dimethylaminopurine
9-(3-ethyl-D-ribofuranosyl)-2-methylaminopurine
9-(3-ethyl-D-ribofuranosyl)-6-methylaminopurine
9-(3-ethyl-D-ribofuranosyl)-2,6-dimethylaminopurine
9-(3-methyl-D-ribofuranosyl)-2-ethylaminopurine
9-(3-methyl-D-ribofuranosyl)-6-ethylaminopurine
9-(3-methyl-D-ribofuranosyl)-2,6-diethylaminopurine
9-(3-ethyl-D-ribofuranosyl)-2-ethylaminopurine
9-(3-ethyl-D-ribofuranosyl)-6-ethylaminopurine
9-(3-ethyl-D-ribofuranosyl)-2,6-diethylaminopurine
9-(3-propyl-D-ribofuranosyl)-2-ethylaminopurine
9-(3-propyl-D-ribofuranosyl)-6-ethylaminopurine
9-(3--propyl-D-ribofuranosyl)-2,6-diethylaminopurine
9-(3-methyl-D-ribofuranosyl)-2-hydroxypurine
9-(3-methyl-D-ribofuranosyl)-6-hydroxypurine
9-(3-methyl-D-ribofuranosyl)-2,6-dihydroxypurine
9-(3-ethyl-D-ribofuranosyl)-2-hydroxypurine
9-(3-ethyl-D-ribofuranosyl)-6-hydroxypurine
9-(3-ethyl-D-ribofuranosyl)-2,6-dihydroxypurine
9-(3-methyl-D-ribofuranosyl)-2-methyl-6-aminopurine
9-(3-ethyl-D-ribofuranosyl)-2-amino-6-methylpurine
9-(3-methyl-D-ribofuranosyl)-2-methyl-6-methylaminopurine
9-(3-methyl-D-ribofuranosyl)-2-methylamino-6-methylpurine
9-(3-methyl-D-ribofuranosyl)-2-amino-6-methylaminopurine
9-(3-methyl-D-ribofuranosyl)-2-methyl-6-hydroxypurine
9-(3-methyl-D-ribofuranosyl)-2-hydroxy-6-methylpurine
9-(3-methyl-D-ribofuranosyl)-2-amino-6-hydroxypurine
9-(3-methyl-D-ribofuranosyl)-2-hydroxy-6-aminopurine
9-(3-methyl-D-ribofuranosyl)-2-methylamino-6-hydroxypurine
9-(3-methyl-D-ribofuranosyl)-2-hydroxy-6-methylaminopurine
9-(3-methyl-D-ribofuranosyl)-2-dimethylaminopurine
9-(3-methyl-D-ribofuranosyl)-6-dimethylaminopurine
9-(3-methyl-D-ribofuranosyl)-2-methylamino-6-dimethylaminopurine
9-(3-methyl-D-ribofuranosyl)-2-mercaptopurine
9-(3-methyl-D-ribofuranosyl)-6-mercaptopurine
9-(3-methyl-D-ribofuranosyl)-2,6-dimercaptopurine
9-(3-methyl-D-ribofuranosyl)-2-methyl-6-mercaptopurine
9-(3-methyl-D-ribofuranosyl)-6-methyl-2-mercaptopurine
9-(3-methyl-D-ribofuranosyl)-2-mercapto-6-methylmercaptopurine
9-(3-methyl-D-ribofuranosyl)-2,6-dichloropurine
9(3-methyl-D-ribofuranosyl)-2-chloropurine

9-(3-methyl-D-ribofuranosyl)-2-bromopurine
9-(3-methyl-D-ribofuranosyl)-6-bromopurine
9-(3-methyl-D-ribofuranosyl)-6-chloropurine
9-(3-methyl-D-ribofuranosyl)-2,6-dibromopurine.

Compounds of the present invention have a variety of valuable uses. They are capable of inhibiting ribonucleic acid (RNA) synthesis, for example, acid insoluble RNA synthesis, in Ehrlich ascites cells and KB cells. In *in vitro* tests, the growth of KB cells and chick embryo fibroblast cells are markedly suppressed as is the inhibition of hypoxanthine incorporation into acid insoluble RNA. Compounds in accordance with the present invention are therefore useful as anti-metabolites, as cell growth inhibitors and for the study of metabolism systems. They also demonstrate favorable cytotoxicity characteristics considered with their cell growth depression.

Compounds of the present invention may also be converted to nucleotides by treatment with phosphoric acid derivatives in accordance with known techniques. As such, they are useful in a formulation of media for selective culturing of animal tissue cells. These nucleotides may also be useful in the study of nucleic acid metabolism.

The following examples in which "Dowex" is a trade mark illustrate the invention: amplifying data appear in the preparations.

PREPARATION 1

Preparation of 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide

This preparation shows the synthesis of a novel starting material used in the preparation of the compound of the present invention.

A Grignard reagent prepared from 690 mg. (28.4 millimoles) of magnesium and 3.85 g. (27.5 millimoles) of methyl iodide in 32 ml. of dry ether is added to a stirred solution of 1.0 g. (3.42 millimoles) of 1,2-O-isopropylidine-5-O-benzoyl-α-D-*erythro*-3-pentulofuranose in 100 ml. of dry ether at 5°C. After about 3 hours the reaction mixture is poured into a mixture of 50 g. of ammonium chloride, 200 ml. of ice and water, and 200 ml. of ether. The layers are separated and the aqueous phase is extracted with two 150-ml. portions of ether. The dried ($MgSO_4$) ethereal solution is concentrated to dryness and the residue (1.24 g.) is crystallized from ether. A total of 524 mg. of 1,2-O-isopropylidene-5-O-benzoyl-3-methyl-α-D-ribofuranose is obtained.

A solution of 1.0 g. (3.25 millimoles) of 1,2-O-isopropylidene-5-O-benzoyl-3-methyl-α-D-ribofuranose in 25 ml. of 3% methanolic hydrogen chloride is kept at 25°C. for 75 minutes. The hydrogen chloride is neutralized by the portionwise addition of 2.5 g. (30 millimoles) of sodium bicarbonate. The mixture is filtered and the solid is washed with methanol. The filtrate plus washings are concentrated and the residue is leached with three 50-ml. portions of methylene chloride. The methylene chloride solution is treated with a small amount of decolorizing carbon, filtered and concentrated. The residue is chromatographed on 20 g. of silica gel. Elution with ethyl acetate-chloroform (1:9) gives 290 mg. of crude methyl 5-O-benzoyl-2,3-O-isopropylidene-3-methyl-β-D-ribofuranoside. Further elution with ethyl acetate-chloroform (1:9) gives about 240 mg. of mixed products. Finally, elution with ethyl acetate-chloroform (1:1) gives 420 mg. (46%) of methyl 5-O-benzoyl-3-methyl-D-ribofuranoside as an oil.

The 420 mg. (1.49 millimoles) of methyl 5-O-benzoyl-3-methyl-D-ribofuranoside from above is dissolved in 7.5 ml. of dry pyridine and cooled in an ice bath. A solution of 463 mg. (3.3 millimoles) of benzoyl chloride in 2.5 ml. of dry chloroform ($CHCl_3$) is added dropwise with stirring. The reaction mixture is kept at 25°C. for 24 hours and 0.5 ml. of water is added. After 30 minutes the mixture is poured onto 30 ml. of ice and water and extracted with three 30-ml. portions of chloroform. The chloroform solution is washed with cold 5% hydrochloric acid until the washings are acidic and finally with saturated sodium chloride solution. The dried ($MgSO_4$) chloroform solution is concentrated to dryness and a residue of methyl 2,5-di-O-benzoyl-3-methyl-D-ribofuranoside is obtained.

A solution of 230 mg. (0.595 millimole) of methyl 2,5-di-O-benzoyl-3-methyl-D-ribofuranoside in 3 ml. of dry pyridine is treated with a solution of 90 mg. (0.64 mmole) of benzoyl chloride in 1 ml. of dry chloroform. The mixture is heated at 100°C. for 16 hours, cooled to 25°C., treated with 0.5 ml. of water and warmed to 40°C. The cooled mixture is added to ice and water and extracted with three 50-ml. portions of chloroform. The chloroform is washed with 10% hydrochloric acid until the washings are acidic and with 10% sodium bicarbonate. The dried ($MgSO_4$) chloroform layer was concentrated and the residue (370 mg.) is chromatographed on

8 g. of silica gel. Methyl 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranoside (280 mg.; 95%) is obtained.

A solution of 2 g. (4.04 millimoles) of methyl-2,3,5-tri-O-benzoyl-D-ribofuranoside in 10 ml. of acetic acid is cooled in an ice bath and 1 ml. of acetyl bromide is added followed by 10 ml. of a 33% solution of hydrogen bromide in acetic acid. After 15 minutes at 0—5°C. the solution is kept at 25°C. for 35 minutes. Concentration of the solution gives a residual oil which is freed of last traces of hydrogen bromide by distilling 3 portions of dry toluene and 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide is obtained.

PREPARATION 2

Preparation of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-2-acetamido-6-hydroxypurine

25 ml. of xylene is distilled from a suspension of 5.95 g. of (0.014 M) of chloromercuri 2-acetamido-6-hydroxypurine in 175 ml. of xylene to remove the last traces of water. The suspension is cooled to 25°C. and 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide prepared from 6.85 g. (0.014 M) of methyl 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranoside in 25 ml. of dry xylene is added. The mixture is stirred and heated at a temperature of from about 50°C. to about 100°C. The solid changes from a granular form to flocculent. After being refluxed for one hour, the hot mixture is filtered, which removes the undissolved solids. Leaching the solids with three 50-ml. portions of boiling chloroform removes additional soluble product and leaves insoluble starting chloromercuri derivatives and inorganic salts. The original filtrate is diluted with two volumes of petroleum ether and the solid which separates is dissolved in the chloroform solution obtained above. The chloroform solution plus an additional 100 ml. is washed with two 75-ml. portions of 30% potassium iodide solution and two 75-ml. portions of water. The dry chloroform layer is concentrated and 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-2-acetamido-6-hydroxypurine is obtained.

PREPARATION 3

Preparation of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-N-methylbenzamidopurine

150 ml. of xylene is distilled from a suspension of 9.5 g. (19.5 millimoles) of chloromercuri 6-N-methylbenzamidopurine in 500 ml. of xylene. The mixture is cooled and a solution of 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide (from 6.9 g. [14.1 millimoles] of methyl-2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl) in 50 ml. of dry xylene is added. The reaction mixture is stirred and refluxed for 30 minutes. The hot mixture is filtered and 3 g. of unreacted starting chloromercuri purine is recovered. The filtrate is concentrated to dryness and the residual oil in 300 ml. of chloroform is washed with two 80-ml. portions of 30% potassium iodide solution and two 80-ml. portions of water. The residual oil obtained after removal of the chloroform is chromatographed on a short column of 140 g. of acid washed alumina in 9 to 1 benzene-chloroform. Fractions are combined and concentrated giving 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-N-methylbenzamidopurine.

PREPARATION 4

Preparation of β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-chloropurine

100 ml. of xylene is distilled from a suspension of 6.55 g. (16.8 millimoles) of chloromercuri-6-chloropurine in 460 ml. of xylene in order to remove the last traces of water. A solution of 8.25 g. (16.8 millimoles) of β-2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide in 40 ml. of dry xylene is added to the stirred suspension at 25°C. The mixture is refluxed for 2 hours. The hot mixture is filtered to remove insoluble material. The filtrate is concentrated to 150 ml. and diluted with 300 ml. of petroluem ether and dried. The crude product is dissolved in 300 ml. of hot chloroform and washed with two 80-ml. portions of 30% potassium iodide solution and two 80-ml. portions of water. The dried ($MgSO_4$) chloroform layer is concentrated, and β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-chloropurine is obtained. The product is purified by chromatography on a short alumina column in chloroform.

PREPARATION 5

Preparation of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-2,6-dibenzamidopurine

100 ml. of xylene is distilled from a suspension of 5.01 g. (8.43 millimoles) of chloromercuri 2,6-dibenzamido purine in 370 ml. of xylene to remove last traces of

water. The suspension is cooled to room temperature in a solution of 4.15 g. (8.43 millimoles) of 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide in 37 ml. of dry xylene is added while the suspension is being stirred. The mixture is refluxed for 2 hours and filtered hot which removes insoluble material. The filtrate is diluted with 400 ml. of petroleum ether and cooled in an ice bath. The solid is removed and dried. The product is obtained as a complex with mercuric halide. The product is dissolved in 100 ml. of chloroform and washed with two 40-ml. portions of 30% potassium iodide solution and two 40-ml. portions of water. The dried ($MgSO_4$) chloroform solution is concentrated at reduced pressure to give 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-2,6-di-benzamido purine.

PREPARATION 6

Preparation of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-methylpurine

A suspension of 317 g. (10 millimoles) of chloromercuri 6-methylpurine [Davoll and Lowy, J. Am. Chem. Soc. *73* 1650 (1951)] in 200 ml. of xylene is dried by distilling about 50 ml. of xylene. The cooled suspension is treated with 5.39 g. (10 millimoles) of 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide dissolved in 30 ml. of dry xylene. The mixture is stirred and refluxed for 2 hours and while hot it is filtered to remove insoluble material. The filtrate is diluted with 4 volumes of petroleum ether and, after being cooled for about 2 hours in an ice bath, the mixture is filtered. The solid is dissolved in 200 ml. of chloroform and washed with two 30-ml. portions of 20% aqueous potassium iodide solution. The chloroform layer is dried (anhydrous $MgSO_4$) and concentrated to a residue of amorphous 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-methylpurine.

PREPARATION 7

Preparation of β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-benzamidopurine

A suspension of 1.92 g. (4.04 millimoles) of finely ground chloromercuri 6-benzamidopurine in 170 ml. of xylene is dried by distilling 90 ml. of xylene. The mixture is cooled and a solution of β-2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide [made from 2.0 g. (4.04 millimoles) of β-methyl 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranoside] in 20 ml. of dry xylene is added. The mixture is stirred and refluxed for 40 minutes. The hot mixture is filtered and the solid is washed with 25 ml. of hot xylene. The filtrate and washings are diluted with 400 ml. of petroleum ether, and after being kept at 5°C. for 20 hours, the mixture is filtered. The solid is dissolved in 150 ml. of hot chloroform and the solution is washed with two 30-ml. portions of 30% potassium iodide solution and two 30-ml. portions of water. Concentration of the dried chloroform layer gives amorphous product which is cromatographed on 40 g. of alumina in benzene-chloroform (1:9). Fractions showing only one zone (R_f 0.28) after thin layer chromatography on alumina in the same solvent mixture are combined and concentration of the solvent gives 920 mg. of β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-benzamidopurine as an amorphous solid.

EXAMPLE 1

Preparation of β-9-(3-methyl-D-ribofuranosyl)-6-dimethylaminopurine

A suspension of 1.0 g. (1.6 millimole) of β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-chloropurine as prepared in Preparation 4 in 25 ml. of methanol containing 6.5 g. of dimethylamine is heated for 10 hours in a sealed tube at 100°C. The solution is concentrated at reduced pressure and the residue is dissolved in 25 ml. of water. The water solution is washed with five 8-ml. portions of benzene and then treated with 2 g. of Dowex II—X8 which is a strongly basic anion exchange resin having a styrene divinylbenzene polymer matrix and containing quaternary ammonium groups. It has an average particle size in the range of 50—100 mesh. It is manufactured by the Dow Chemical Co. of Midland, Michigan (See Pate 1576, 7th Ed., Merck Index, Merck & Co., Inc., Rahway, N. J. The resin is filtered and washed with three 25-ml. portions of water. The filtrate is concentrated to dryness and β-9-(3-methyl-D-ribofuranosyl)-6-dimethylaminopurine is obtained.

EXAMPLE 2

Preparation of 9-(3-methyl-D-ribofuranosyl)-2,6-diaminopurine

A mixture of 1.2 g. (1.4 millimoles) of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-2,6-dibenzamidopurine as prepared in Preparation 5 in 12 ml. of dry methanol is treated with a solution of 97 mg. of (4.2 millimoles) of sodium in 12 ml.

of methanol. The mixture is refluxed for 3 hours and the resultant solution is concentrated at reduced pressure. The residue is dissolved in 24 ml. of water and the pH is adjusted to about 6.5. The aqueous solution is extracted with five 10-ml. portions of chloroform to remove ethyl benzoate and concentrated at reduced pressure to a residue containing 9-(3-methyl-D-ribofuranosyl)-2,6-diaminopurine.

EXAMPLE 3

Preparation of β-9-(3-methyl-D-ribofuranosyl)-purine-6-thiol

A suspension of 1.25 g. (2.0 millimoles) of β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-chloropurine, prepared as in Preparation 4, and 307 mg. (4.0 millimoles) of thiourea in 3 ml. of ethanol is refluxed for 40 minutes. After 5 minutes a clear colorless solution is obtained which becomes yellow in 15 minutes and shortly thereafter colorless crystals of β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-purine-6-thiol crystallize out of solution.

A suspension of 400 mg. (0.65 millimoles) of β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-purine-6-thiol in 3.5 ml. of dry methanol is treated with a solution made from 19.5 mg. of sodium and 3.5 ml. of dry methanol is added. Complete solution occurs immediately. The solution is refluxed for three hours. The solution is concentrated by distillation at reduced pressure and the residue is dissolved in 6 ml. of water and the pH of the solution is adjusted to 9 with acetic acid and the aqueous mixture is extracted with four 1.5 ml. portions of methylene chloride. The water layer is concentrated by distillation to a volume of 4 ml. and the pH is adjusted to 4 with acetic acid. The concentration of the solution gives a residue containing β-9-(3-methyl-D-ribofuranosyl)-purine-6-thiol.

EXAMPLE 4

Preparation of 9-(3-methyl-D-ribofuranosyl)-6-methylaminopurine

A mixture of 1 g. (1.63 millimoles) of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-chloropurine and 8g. of methylamine in 25 g. of dry methanol is heated for ten hours at 100°C. in a sealed tube. The solution is concentrated to dryness at reduced pressure and the residue is dissolved in 25 ml. of water. The water solution is washed with two 5-ml. portions of benzene. The aqueous layer is stirred for 2.5 hours with 3.5 grams of moist Dowex II—X8 (see Example 1), during which time the pH of the solution rises from 7 to 9. The resin is removed and washed with three 15-ml. portions of water. The filtrate and washings are concentrated to a residue containing 9-(3-methyl-D-ribofuranosyl)-6-methylaminopurine.

EXAMPLE 5

Preparation of 9-(3-methyl-D-ribofuranosyl) purine

A solution of 1 g. (1.63 millimoles) of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-chloropurine in 17 ml. of dioxane with 80 mg. (2.0 millimoles) of magnesium oxide and 0.5 g. of 5% palladium on charcoal catalyst is shaken for 98 hours in an atmosphere of hydrogen at 25°C. The mixture is filtered and concentrated by distillation at reduced pressure to a residue containing 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)purine.

A solution of 400 mg. (0.70 millimoles) 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)purine in 8 ml. of dry methanol is treated with a solution made from 23 mg. (1 mg. atom) of sodium and 8 ml. of dry methanol. The pale yellow solution is refluxed for 3 hours and concentrated to dryness at reduced pressure. The residue is dissolved in 15 ml. of water and the pH is adjusted to 6.5 with acetic acid. The solution is extracted with four 5-ml. portions of chloroform and the water phase is concentrated to dryness at reduced pressure to a residue containing 9-(3-methyl-D-ribofuranosyl)purine.

EXAMPLE 6

Preparation of β-9-(3-methyl-D-ribofuranosyl)guanine

About 25 ml. of xylene is distilled from a suspension of 5.95 g. (0.014 mole) of chloromercuri 2-acetamido-6-hydroxypurine in 175 ml. of xylene in order to remove last traces of water. The suspension is cooled to 25°C. and β-2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide (prepared from 6.85 g. (0.014 mole) of β-methyl 2,3,5-tri-O-benzoyl-3-methyl-β-D-ribofuranoside) in 25 ml. of dry xylene is added. The mixture is stirred and heated. At about 50°C. to 100°C. the solid changes from a granular form to flocculent. After being refluxed for 1 hour the hot mixture is filtered which removes undissolved solvent. Leaching the solid with three 50-ml. portions of boiling chloroform removes additional soluble product and leaves the insoluble starting chloromercuri derivative and inorganic salts.

The original filtrate is diluted with 2 volumes of petroleum ether and the solid which separates is dissolved in the chloroform solution obtained above. The chloroform solution (plus an additional 100 ml.) is washed with two 75-ml. portions of 30% potassium iodide and one 75-ml. portion of water. The dried chloroform layer is concentrated and a crude mixture of β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-2-acetamidohypoxanthine is obtained as a glass and purified by column chromatography.

A suspension of 800 mg. (1.23 millimoles) of β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-2-acetamidohypoxanthine in 8 ml. of dry methanol is treated with a solution made from 105 mg. (4.5 mg. atom) of sodium and 8 ml. of dry methanol and the mixture is refluxed for two hours. The mixture is concentrated to dryness. The residue is dissolved in 35 ml. of water and the pH is adjusted to 7 by the addition of acetic acid. The clear solution is washed with three 8-ml. portions of chloroform and the aqueous layer is concentrated to a residue of β-9-(3-methyl-D-ribofuranosyl) guanine.

EXAMPLE 7

Preparation of β-9-(3-methyl-D-ribofuranosyl)-6-chloropurine

A solution of 479 mg. (0.1 mole) of β-9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-chloropurine, as prepared in Preparation 4, in 20 ml. of cold methanol containing 2 grams of anhydrous ammonia is kept at 5°C. for 20 hours. The solution is concentrated at reduced pressure and at a temperature of less than 20°C. The residue is recrystallized from methanol to give β-9-(3-methyl-D-ribofuranosyl)6-chloropurine.

EXAMPLE 8

Preparation of 9-(3-methyl-D-ribofuranosyl)-6-methylamino purine

About 150 ml. of xylene is distilled from a suspension of 9.5 g. (19.5 millimoles) of chloromercuri-6-N-methyl-benzamido purine in 500 ml. of xylene. The mixture is cooled and a solution of 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide (from 6.9 g. (14.1 millimole) of methyl 2,3,5-tri-O-benzoyl-3-methyl-β-D-ribofuranoside) in 50 ml. of dry xylene is added. The reaction mixture is stirred and refluxed for 30 minutes. The hot mixture is filtered and 3 grams of unreacted starting chloromercuri purine is recovered. The filtrate is concentrated to dryness and the residual oil in 300 ml. of chloroform is washed with two 100-ml. portions of 30% potassium iodide and two 100-ml. portions of water. The residual oil obtained after removal of the chloroform is chromatographed on a short column of 140 g. of acid-washed alumina in benzene-chloroform (1:9). Fractions containing only product are combined and concentrated giving 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-N-methylbenzamidopurine as a glass.

A suspension of 3.9 g. (5.55 millimoles) of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-N-methyl-benzamidopurine in 40 ml. of dry methanol is treated with a solution made from 175 mg. (7.6 mg. atom) of sodium in 40 ml. of dry methanol and the solution is refluxed for 3.5 hours. The methanol is removed and the solution of the residue in 76 ml. of water is neutralized (pH 7.0) with acetic acid and washed with three 10-ml. portions of chloroform. The aqueous layer is concentrated by distillation to a residue of 9-(3-methyl-D-ribofuranosyl)-6-methylaminopurine.

EXAMPLE 9

Preparation of 9-(3-methyl-D-ribofuranosyl)-6-ethylaminopurine

A solution of 2.0 g. (3.26 millimoles) of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-chloropurine as prepared in Preparation 4, in 30 ml. of ethanol containing 12 ml. of ethyl amine is heated in a sealed tube at 100°C. for 10 hours. After removing the solvent, the residue is dissolved in 60 ml. of water and extracted with three 15-ml. portions of ether. The aqueous layer (pH 6.5) is stirred for 1 hour with 2.5 g. of Dowex II—X8 (see Example 1). The resin is removed and washed with four 10-ml. portions of water. The combined filtrate and washings are concentrated to a residue of 9-(3-methyl-D-ribofuranosyl)-6-ethylaminopurine.

EXAMPLE 10

Preparation of 9-(3-methyl-D-ribofuranosyl)-6-methylthiopurine

A boiling mixture of 605 mg. (2 millimoles) of 9-(3-methyl-D-ribofuranosyl)-6-chloropurine, as prepared in Preparation 4, in 30 ml. of anhydrous methanol is treated with a solution prepared by saturating 20 ml. of 0.1 N sodium methoxide in methanol with methyl mercaptan. After being refluxed for about 30 minutes the solution is cooled and concentrated to dryness. The residue is dissolved in hot water and on cooling, 9-(3-methyl-D-ribofuranosyl)-6-methylthiopurine separates.

EXAMPLE 11

Preparation of 9-(3-methyl-D-ribofuranosyl)-6-methylpurine

A mixture of 590 mg. (1 millimole) of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-methylpurine, as prepared in Preparation 6, and 50 ml. of dry methanol is treated with a solution prepared from 23 mg. (1 mg. atom) of sodium and 10 ml. of dry methanol. The mixture is refluxed for 4 hours and concentrated to dryness. The residue is dissolved in 30 ml. of water and neutralized (pH 7) with acetic acid. When the water layer is concentrated to a small volume and cooled, 9-(3-methyl-D-ribofuranosyl)-6-methylpurine precipitates.

EXAMPLE 12

Preparation of β-3′-methyladenosine

A mixture of 1.26 g. (1.8 millimoles) of β-9-(2,3,5-tri-O-benzoyl-3-methyl-β-D-ribofuranosyl) 6-benzamido purine as prepared in Preparation 7 and 13 ml. of dry methanol is treated with a solution of sodium methoxide prepared from 70 mg. (3 millimoles) of sodium and 3 ml. of methanol. After the mixture is refluxed for 2 hours, it is concentrated and the residue is dissolved in 50 ml. of water. The pH is adjusted from 11.5 to 5.2 with a few drops of acetic acid. The solution is extracted with five 20-ml. portions of chloroform and the water layer is filtered and concentrated to dryness. The residue is dissolved in methanol and 430 mg. of impure amorphous product is precipitated with ether. The filtrate is concentrated to dryness and the residue is crystallized from a water solution. Recrystallization from 0.7 ml. of water gives 126 mg. of 3′-methyladenosine.

The following Table demonstrates the ability of one of the compounds of the present invention to inhibit nucleic acid biosynthesis. The method employed for the hypoxanthine test is that described by H. T. Shigeura and C. N. Gordon in *Journal of Biological Chemistry*, 237, 1932 (1962). The method employed for the cytotoxicity is that described by C. O. Getterman, *et al* Journal of Medicinal Chemistry Volume 8, Page 664, 1965.

The results of this test are shown in the following Table I.

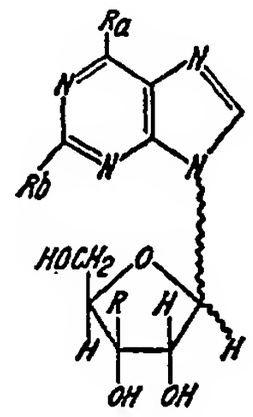
TABLE I

Hypoxanthine-8-C^{14} Incorporation into Acid Insoluble RNA			Cytotoxicity (ED_{50}, γ/ml)	
	γ/ml.	% Inhibition	KB Cells	Chick Embryo FibroblastCells
9-(3-Methyl-D-ribofuranosyl)-6-amino purine	100 50	16 9	3—10	10—30

The results shown in the foregoing Table I are expressed as percent inhibition of the incorporation of hypoxanthine-8-C^{14} as compared to a controlled experiment carried out without the inhibitor. The cytotoxicity of the compound of the present invention was determined by using chick embryo fibroblast cells and KB cells. In this test the KB cells are tumor cells and the chick cells are normal cells and it is of particular interest that the compound of the present invention was more effective in inhibiting the growth of the tumor cells than the chick cells. It will be noted from the Table that the compound of the present invention is about three times as active in KB cells as in the chick embryo system.

WHAT WE CLAIM IS:—

1. A compound of the formula:—



where R is a C_{1-5} alkyl radical and each of R_a and R_b is a hydrogen or halogen atom or a hydroxy, C_{1-5} alkyl, amino, C_{1-5} alkylamino, di(C_{1-5} alkyl)amino, halo, mercapto or C_{1-5} alkyl mercapto radical.

2. A compound according to claim 1 in which R is a methyl radical.

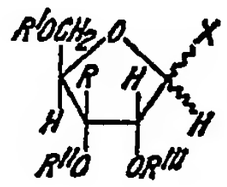
3. A compound according to claim 1 in which R is an ethyl radical.

4. β-3′-methyladenosine.

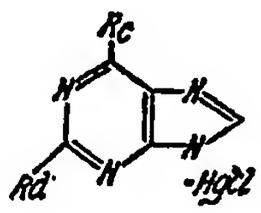
5. β-9-(3-Methyl-*D*-ribofuranosyl)guanine.

6. β-9-(3-Methyl-*D*-ribofuranosyl)-purine-6-thiol.

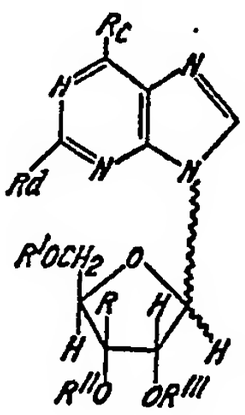
7. The process that comprises A reacting a compound of the formula:—



where each of R′, R″ and R‴ is an acyl group and X is a halogen atom with a compound having the formula:—



where each of R_c and R_d is a halogen or hydrogen atom or a hydroxy, C_{1-5} alkyl, acylamino or acyl C_{1-5} alkylamino radical to produce a compound of the formula:—



IV

where R, R_c, R_d, R′, R″ and R‴ are as defined above and,

B (a) when each of R_c and R_d is a hydrogen or halogen atom or a hydroxy, C_{1-5} alkyl, acylamino or acyl C_{1-5} alkylamino radical subjecting compound IV to basic solvolysis or;

(b) when one of R_c and R_d is a halogen atom and the other of R_c and R_d is a hydrogen or halogen atom or a C_{1-5} alkyl, acylamino or acyl C_{1-5} alkylamino radical subjecting compound IV to aminolysis, mercaptolysis or hydrogenation and solvolysis, to produce a compound as claimed in claim 1, in which process if R_c or R_d in compound IV is an acylamino or acyl C_{1-5} alkylamino group it is converted to an amino or C_{1-5} alkylamino group during step B.

8. A process according to claim 7 in which Step (b) is solvolysis and the solvolysing agent is an alkali or alkaline-earth metal hydroxide or alkoxide, a solution of ammonia an amine or a substituted amine in a C_{1-4} alcohol.

9. A process according to claim 7 or 8 in which the solvolysis is carried out at a temperature of from 65° to 90°C.

10. A process according to claim 7 in which Step (b) is aminolysis and the aminolysing agent is a C_{1-5} alkylamine or a di(C_{1-5} alkyl) amine.

11. A process according to claim 7 or 10 in which the aminolysis is carried out at a temperature of from 85° to 110°C.

12. A process according to claim 7 in which Step (b) is mercaptolysis and the mercaptolysing agent is thiourea or an alkali or alkaline-earth metal salt of a C_{1-5} alkyl mercaptan, provided that if the mercaptolysing agent is thiourea it is necessary to subject the product to solvolysis to produce a compound as claimed in claim 1.

13. A process according to claim 7 or 12 in which the mercaptolysis step is carried out at a temperature of from 65° to 90°C.

14. A process according to claim 7 in which Step (b) is hydrogenation followed by solvolysis in which palladium on charcoal is used as a catalyst in the hydrogenation step.

15. A process according to any one of claims 7—14 in which Step (a) is carried out using stoichiometric quantities of the purine and ribofuranosyl halide compounds.

16. A process according to any one of claims 7—15 in which Step (a) is carried out at a temperature of from 100° to 140°C.

17. A process according to any one of claims 7—16 in which Step (a) is carried out in benzene, dibutylether, cyclohexane, toluene or xylene.

18. A process according to claim 7 in which Step (a) is carried out at a temperature of from 25°C., to 50°C., for a period of time from about 15 minutes to about 5 hours in the presence of a solvent; the basic solvolysis is carried out at a temperature of from 5°C., to 150°C., for a period of time from about 15 minutes to about 5 hours; the aminolysis is carried out at a temperature of from 25°C., to 150°C., for a period of time from about 15 minutes to about 5 hours; and the mercaptolysis is carried out at a temperature of from 65°C., to 90°C., for a period of time from about 15 minutes to about 5 hours.

19. The process that comprises treating β-2,3,5-tri-O-benzoyl-3-methyl-*D*-ribofuranosyl bromide with chloromercuri 6-benzamidopurine in the presence of xylene at reflux for about 40 minutes and then held at 5°C., for about 20 hours to produce β-9-(2,3,5-tri-O-benzoyl-3-methyl-β-*D*-ribofuranosyl)-6-benzamidopurine and refluxing said β-9-(2,3,5-tri-O-benzoyl-3-methyl-β-*D*-ribofuranosyl)-6-benzamidopurine with sodium methoxide for about 2 hours in methanol to produce β-3′-methyladenosine.

20. A process according to claim 7 substantially as hereinbefore described in any one of the examples.

21. A compound according to claim 1 when prepared by a process according to any one of claims 7—20 or by an obvious chemical equivalent of such a process.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.